LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cromiva
(miglustat)

SE/H/1359/01/DC

This module reflects the scientific discussion for the approval of Cromiva. The procedure was finalised at 2014-09-23. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

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I. INTRODUCTION

The application for Cromiva, 100 mg, capsule hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Glenmark Pharmaceuticals Europe Limited apply through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DE, SK, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is the centrally authorised Zavesca, 100 mg, hard capsule authorised in EU since 2002, with Acetelion Registration Ltd as marketing authorisation holder.
The reference product used in the bioequivalence study is Zavesca, 100 mg, hard capsule from the Polish market with Acetelion Registration Ltd as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Cromiva is presented in the form of capsules containing 100 mg of miglustat. The excipients are sodium starch glycolate type A, povidone, magnesium stearate, gelatin and titanium dioxide. The capsules are packaged in Aclar-Alu (PVC/PE/PCTFE-Alu) blisters.

II.2 Drug Substance

Miglustat does not have a monograph in the Ph Eur.

Miglustat is a white to off-white solid soluble in water and methanol. The structure of Miglustat has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality are presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Cromiva, hard capsule, 100 mg, is formulated using excipients described in the current Ph Eur. Gelatine is of animal origin. A BSE/TSE Statement of gelatine is provided.
All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

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The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process is a relatively straight-forward process consisting of granulation; blend; encapsulation and packaging. Proposed in-process controls are acceptable. Process validation has not been conducted, but will be performed on three commercial batches prior to marketing and a protocol has been provided. A process validation protocol has been provided.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precaution.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The oral bioavailability of miglustat has not been determined, but the substance is rapidly absorbed. Following an oral dose of miglustat maximal plasma concentrations occur at approximately 2 hours.
Concomitant administration of food decreases the rate of absorption of miglustat but has no statistically significant effect on the extent of absorption, and therefore there are no restrictions with respect to food in the SmPC of the originator. The kinetics of miglustat appears to be dose linear and time independent. The terminal half-life is 6-7 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Cromiva, 100 mg, hard capsules with Zavesca, 100 mg, hard capsules, by Actelion Registration Ltd, UK from the Polish market under fasting conditions. The study was conducted between 23rd November and 5th December 2012. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of miglustat were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence study, the applied product is considered bioequivalent with Zavesca.

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IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

A user consultation with target patient groups on the package information leaflets (PIL) have been performed on the basis of a bridging report making reference to the product Zavesca, 100mg hard capsule, approved via the Central procedure (EMEA/H/C/435).
Regarding lay-out: the applicant has stated that the PLs will be prepared in their standard in-house style, that has been established and readable in previous user tests.

The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Cromiva, 100 mg, capsule hard, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Cromiva, 100 mg, capsule hard, was successfully finalised on 2014-09-23.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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